Impact of the Highly Selective D1-Like Partial Dopamine Agonist Tavapadon on Daytime Sleepiness: Evidence From a Phase 2 Clinical Trial

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CONCLUSIONS

- Up to 15 weeks of treatment with tavapadon flexible dosing up to 15 mg QD was not associated with significant differences from placebo in ESS score changes from baseline
  - The selectivity of tavapadon for D1/D5 receptors may help avoid sleep effects commonly associated with D2/D3 agonists
- The effects of tavapadon on daytime sleepiness will be further characterized in ongoing phase 3 trials[15-18]

INTRODUCTION

- D2/D3–selective dopamine agonists (DAs) commonly used in the treatment of Parkinson's disease (PD) can be associated with increased incidence of somnolence and excessive daytime sleepiness (EDS) compared with other therapies[1]
- The sleep effects of currently available DAs are thought to be driven by high affinity for D2/D3 receptors[2-4]
  - The relative risk (95% confidence interval [CI]) of somnolence relative to placebo for pramipexole and ropinirole was 4.98 (1.79, 13.89),[5] and 1.42 (1.14, 1.77) for rotigotine transdermal patch[6]
  - The use of DAs pramipexole, pergolide, or ropinirole was found to be predictive of falling asleep while driving (odds ratio [OR], 3.08; *P*=0.003)[7]
- Tavapadon is a highly selective D1/D5 dopamine agonist being developed as an orally administered, once-daily, symptomatic treatment for PD[6] that may avoid somnolence and daytime sleepiness related to D2/D3 receptor agonism
  - Tavapadon was associated with significant motor improvements compared with placebo (*P*=0.0407) and was well tolerated during the 15-week treatment period[8]

OBJECTIVE

- To report daytime sleepiness data from the phase 2 clinical trial of tavapadon in participants with early-stage Parkinson's disease (PD) utilizing the Epworth Sleepiness Scale (ESS)

METHODS

CLINICAL TRIAL

- The ESS was assessed at baseline, Week 9, and Week 15 during a phase 2, double-blind, randomized, placebo-controlled, flexible-dose trial of tavapadon in early-stage Parkinson's disease (NCT02847650)[8] (**Figure 1**)

EPWORTH SLEEPINESS SCALE

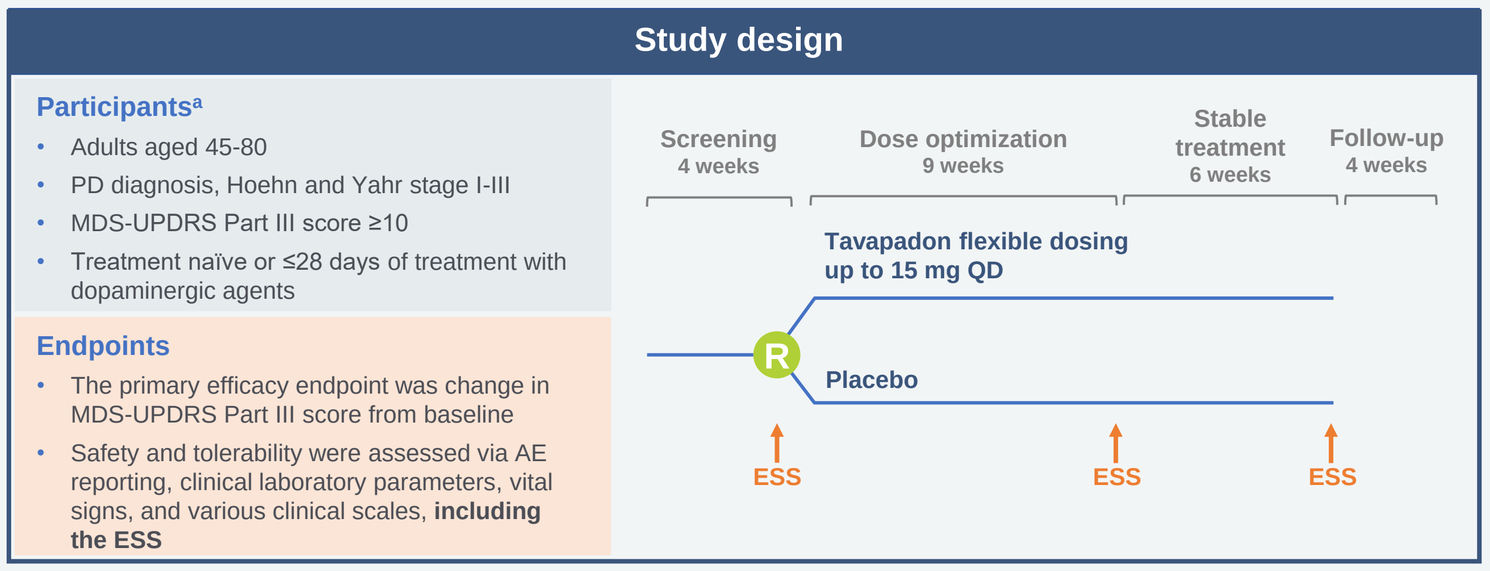
- The ESS is an 8-item, self-administered scale assessing the likelihood of dozing off in various situations[9] (**Figure 2**; **Table**)
  - Each item is scored from 0 (no chance of falling asleep) to 3 (high chance of falling asleep)
  - Total scores range from 0-24; scores >10 indicate excessive daytime sleepiness (EDS)[10]

Table. Example ESS Score Changes With D2/D3 DA Treatment in Clinical Studies of PD[11-14]

DA	Mean ESS score change (DA)	Mean ESS score change (placebo)	Treatment duration
Pramipexole monotherapy	+1.2 (IR)[11,12]	+0.3[11] to -0.6[12]	33 weeks[11]; 18 weeks[12]
	+1.5 (ER)[12]	-0.6	18 weeks
	+1.8 (ER)[11]	+0.3	33 weeks
Rotigotine patch with or without other dopamine therapy	+1.5[13]	N/A	20.6 weeks
	-4.5[14]	N/A	12 weeks

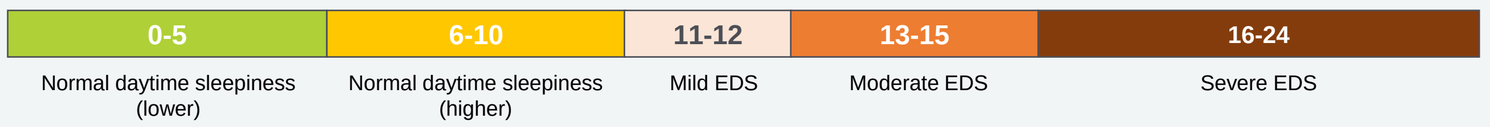
DA, dopamine agonist; ER, extended release; ESS, Epworth Sleepiness Scale; IR, immediate release; PD, Parkinson's disease.

Figure 1. Study design.



[a]This trial was terminated early for reasons unrelated to the trial itself; participants who were already randomized at the time of trial termination were allowed to complete all visits. AE, adverse event; ESS, Epworth Sleepiness Scale; MDS MDS-UPDRS, Movement Disorder Society Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; QD, once daily.

Figure 2. ESS score range.[10]



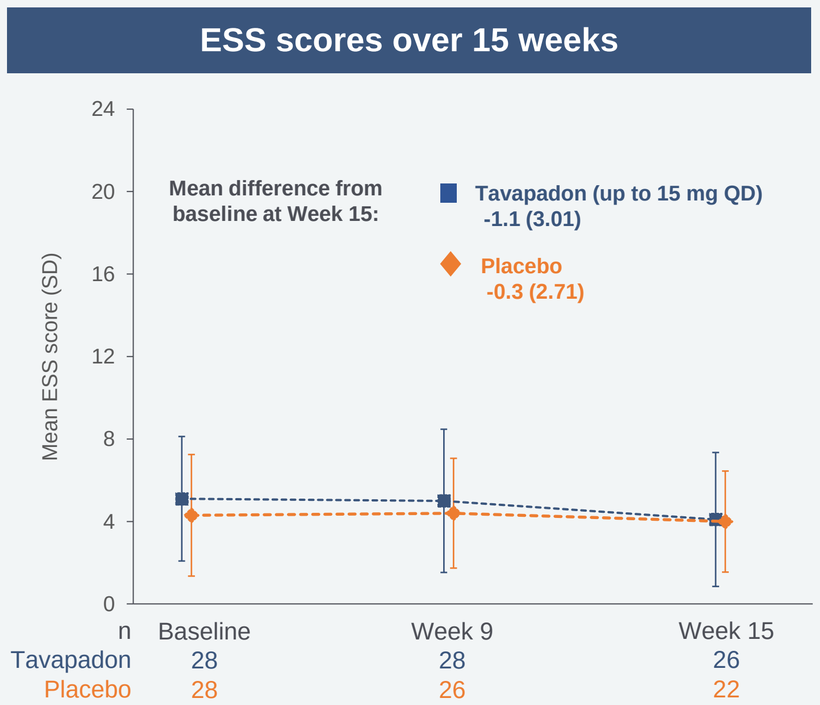
EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale.

RESULTS

ESS SCORES

- No significant changes in ESS scores were observed with 15 weeks of tavapadon flexible dosing (**Figure 3**)
- In a mixed model repeated measures (MMRM) analysis, there were no significant differences in changes in ESS scores from baseline to Week 15 with tavapadon flexible dosing up to 15 mg QD (least-squares mean [SE] difference vs placebo, -0.7 [0.69]; *P*=0.3043)
  - The MMRM analysis included treatment, visit, treatment-by-visit interaction, baseline, baseline-by-visit interaction, geographic region, and concurrent anti-PD medication (Yes/No) at randomization; response variable is change from baseline
- Up to 15 weeks of treatment with tavapadon flexible dosing up to 15 mg QD was not associated with significant differences in ESS score change from baseline
  - Selectivity of tavapadon for D1/D5 receptors may avoid sleep effects commonly associated with D2/D3 agonists
- The effects of tavapadon on daytime sleepiness will be further characterized in ongoing phase 3 trials[15-18]

Figure 3. ESS scores over the course of the trial.



ESS, Epworth Sleepiness Scale; QD, once daily; SD, standard deviation.

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AUTHOR DISCLOSURES:

All authors are employees of Cerevel Therapeutics and may hold stock or equity awards in the company.

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